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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,694	12/21/2004	Michael Chopp	1059.00106	2465

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EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,694	CHOPP, MICHAEL	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 9/29/2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112--New

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering sildenafil or hMCS to ischemic rats, does not reasonably provide enablement for promoting neurogenesis in an ischemic patient in general by administering a phosphodiesterase type 5 inhibitor and cellular therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The invention relates to a method of promoting neurogenesis by administering a phosphodiesterase type 5 inhibitor and cellular therapy to an ischemic patient. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Björklund et al., (Nature Neuroscience 2000). Björklund et al. cellular therapy in regard to treating ischemic stroke is not well settled. Studies involving rats showed success but only under certain conditions e.g. type of cells used, type of injury, environment after administering therapy. (See pg. 541) For these reasons, Björklund et al. cautions, "Without better knowledge of the biological mechanisms of improvement, and optimization of the functional outcome in animal models, cell therapy for patients with ischemic damage is unlikely to develop to the point of therapeutic value." Id.

2. The breadth of the claims

The claims are thus very broad insofar as they suggest that neurogenesis can be promoted by administering phosphodiesterase type 5 inhibitor and cellular therapy in general.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its “full scope”.

In regard to promoting neurogenesis, in the specification at page 32, lines 14-26 applicant describes an experiment where male Wistar rats, subjected to embolic stroke, were administered sildenafil, a PDE type 5 inhibitor. The results indicated that sildenafil increased numbers of bromodeoxyuridine (BrdU)-immunoreactive cells in the subventricular zone and the dentate gyus and the number of immature neurons. Cortical levels of cGMP were also increased. Applicant concluded that sildenafil increaces cGMP, evokes neurogenesis, and reduces neurological deficits in the rats after stroke. However, more guidance is needed in terms of treating humans.

In an article by Johansson, it was stated that regeneration of transectioned central axons have never been convincingly demonstrated in higher mammals and that recovery from stroke seen in humans is likely due to reorganization of cortical networks. (See pg. 223, first paragraph; see also pg. 226 right col. under section heading "Clinical Evidence for Reorganization of Cortical Networks.”) Johansson also makes the case that the improvements in movement in paretic limbs is likely a result of retraining the brain. (See Id.) Johansson also states that stroke recovery in humans is dependant on early rehabilitation. In other words, there is a time element to consider. Applicant's claimed invention reads on promotion of neurogenesis in humans at any stage post-stroke. Given that central axons have never been convincingly demonstrated and that recovery after stroke is time sensitive, it is doubted that neurogenesis can be promoted in humans by simply administering a PDE 5 inhibitor and cellular therapy. More

guidance is needed in regard to treating humans in light of Johansson.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, especially in humans, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for promoting neurogenesis as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

. ***Claim Rejections - 35 USC § 103--New***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black (US 6,043,223) in view of Yoshimura et al., (PNAS 2001).

Black teaches a method of treating abnormal brain tissue in a mammal by administering bradykinin and a cGMP specific phosphodiesterase inhibitor, where the phosphodiesterase inhibitor is zaprinast (type V inhibitor). (See col. 11, claims 10, and

col. 12, claim 12; see also col. 4, line 6.) They teach where the abnormal brain tissue is a result of ischemia. (See col. 3, lines 31-47.) Examples of abnormal brain tissue include gliomas, metastic brain tumors, head injury, meningitis, brain abscess, multiple sclerosis, subarachnoid hemorrhage.

Since the same compound is being administered to the same patient as instantly claimed, the method of Black would be expected to inherently possess the same properties such as promoting neurogenesis to a limited extent, i.e. by increasing brain function in the manner set forth in the specification.

Black does not teach identifying numbers of new neurons.

Yoshimura et al. teach that FGF-2 (fibroblast growth factor-2) promotes neurogenesis after head injury. (See Abstract.) They teach that mammalian neuroprogenitor cells in the adult brain can proliferate and differentiate into neurons after brain injury. (See pg. 5874, left col., second paragraph.) They also teach that identifying neuronal growth via BrdUrd labeling and NeuN expression. (See Abstract.) They studied injury to the hippocampus, a structure involved in spatial, declaragive, and contextual memory, after seizures or ischemic injury. Yoshimura et al. do not teach administration of a phosphodiesterase type 5 inhibitor.

It would have been obvious to a person having ordinary skill in the art at the time of applicants invention to have identified numbers if new neurons, since head injury is often associated with memory loss and regaining memory post treatment would be a way of identifying increased numbers of new neurons.

2) Claims 2, 9, 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black (supra) as applied to claim1, 8, 10 and 12 above, and further in view of Labat (Biomed Pharmacotherapy 2001).

Black differs from the instant claims 2, 9, 11, and 13 insofar as it does not teach further including cellular therapy.

Lat teach the use of stem cells for managing neurological disorders such as stroke, brain trauma and Parkinson's. (See pg. 181, right col., 2nd paragraph.)

It would be prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in prior art." See MPEP 2144.06.

It would have, therefore, been obvious to a person having ordinary skill in the art at the time of applicant's invention to have combined the composition of Black with the stem cells of Labat, since they are both useful for treating head trauma or stroke.

Nonstatutory Obvious-type Double Patenting--New

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 1, 8, 10, 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-8, and 14-17 of copending Application No. 10/075,715. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim a method of affecting the growth of neurons by administering a phosphodiesterase (PDE) type 5 inhibitor. The instant claims differ from the '715 application insofar as they do not claim a specific inhibitor. It would have been obvious to have chosen sildenafil (Viagra®) since it is the best known example of a PDE type 5 inhibitor currently available on the market.

2) Claims 1, 8, 10, 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6 and 7 of copending Application No. 10/018,201. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim a method of affecting the growth of neurons by administering a phosphodiesterase

inhibitor. The patient in the '201 claim set is "ischemic" insofar as the patient is "post stroke." The instant claims differ from the '201 patent insofar as it includes a phosphodiesterase type 5 inhibition, and a step of identifying increased numbers of new neurons. A genus of many species suggests (renders obvious) every species falling within that genus. Therefore, a phosphodiesterase type 5 inhibitor, a species of phosphodiesterase inhibitors, is obvious. In regard to identifying increased numbers of new neurons, because the patient is "post stroke" improvement in the patient post administration would be a way of identifying increased numbers of new neurons.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612